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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,614	04/27/2006	Yvonne Paterson	P-7772-US	4019

49443 7590 01/06/2011

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
01/06/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/541,614	PATERSON ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-21 and 23, 25-30* is/are pending in the application.

4a) Of the above claim(s) *10-19 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-9,20,21,23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 5, 7-21, 23, 25-30 are pending.

Amended Claims 1-2, 5, 7-9, 20-21, 23, 25-27 are under consideration; all other claims stand withdrawn from consideration.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 2, 2010 has been entered.

Objections/Rejections Withdrawn

1. Withdrawn, Claims 1-2, 5-9, 20-21, 23-27 rejected under 35 U.S.C. 112, first paragraph (New Matter), as failing to comply with the written description requirement is herein withdrawn in light of the removal of the functional limitations form the pending claims, the functional limitations not evidencing original descriptive support in the instant Specification at the time of filing.

2. Withdrawn, Claims 1-2, 5-9, 20-21, 23-27 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements, is herein withdrawn in light of the functional limitations that were incomplete have been removed from the claims. . See MPEP § 2172.01.

3. Withdrawn, Claims 1,2,7-9, 20-21, 25-27 rejected under 35 U.S.C. 102(b) as being anticipated by Coulson et al (Vaccine, 1994, Salmonella) is herein withdrawn in light of the independent claims having been amended to recite a Listeria vaccine vector.

1. Withdrawn, Claims 1, 2, 5-9, 20-21, 23-27 under 35 U.S.C. 102(e) as being anticipated by Pawelek et al (US Pat. 6,685,935, effective filing date June 4, 1996) is herein withdrawn in light of the newly submitted combination of claim limitations set forth in the independent claims under consideration.

Response to Arguments

2. Applicant's arguments filed June 2, 2010 have been fully considered but they are not persuasive.

3. Applicant asserts that Pawelek does not describe an enhanced immunogenicity after in vivo passaging.

4. Pawelek et al teaches enhancement of tumor immunity is another potential advance of the bacterial vaccine vectors described (col. 58, lines 10-12).

5. Applicant assets that Pawelek does not describe stabilized virulence of the vector.

6. Pawelek et al does teach stable expression of encoded heterologous genes (see col. 23, lines 61 "stable episomal plasmids"), and the strains selected are "super-infective" which by definition the super-infective strains attach and infect the target cell more quickly and in greater numbers that wild-type cells, and therefore have a stabilized adherence virulence factor that permits that super-infectivity to function more effectively than wild-type strains (see definitions section).

7. Applicant's arguments with respect to claims 1-2, 5, 7-9, 20-21, 23, 25-27 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-2, 5, 7-9, 20-21, 23, 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawelek (US Patent 6,685,935) in view of Vahidy et al (1996, reference cited on US PTO 1449) and Pan et al(1995, reference cited on US PTO 1449).

Pawelek et al teach a method of obtaining (see claims 162-168)

a Listeria (claims 135-136, 143-145; col. 8, line 15)

vaccine vector (col.8, line 15)

stably (see col. 23, lines 61 "stable episomal plasmids") expressing a heterologous antigen (col. 21, lines 44-59 "foreign genes"; col. 4, lines 30-33)

the vector evidencing enhanced immunogenicity (see col. 4, lines 39-41 "Listeria monocytogenes has the ability to deliver a foreign antigen to the immune system and to involve cell-mediated immunity against the same antigen"; Col. 58, lines 10-12 "**Enhancement** of tumor immunity is thus another potential advantage in the use of parasites as tumor-specific therapeutic vectors."; also the super-infective bacterial vectors of Pawelek have "increased tumor specificity... enhanced chemotatic abilities" col. 9, lines 14-18, as well as increased adherence ability "attach and/or infect a target well more readily than the wild type vector" col. 9, lines 49-50), the method comprising the steps of:

Instant claim 1 , 7-8, 20, 25-26: Step a) Administering to an animal (col. 16, lines 30, "mammals", line 33 "mice" and 48 "inoculated into the mouse")

the bacterial vaccine vector (see claim 162, "(a) exposing a mammal having a solid tumor cell cancer to a microorganism for for a time sufficient so that the population of microorganisms can infect the tumor cells"; "(b) isolating a population of super-infective, tumor specific microorganism from the infected tumor cells" (see claim 164 "genetically engineered"; genetically engineered to express and deliver a heterologous antigen(col. 7, lines 59-63 col. 18, lines 18-32; and col. 4, lines 30-33) .

Step b) Passaging the bacterial vaccine vector through the animal (see claim 168 "further comprising: (d) repeating steps (a) and (b) a desired number of times" to obtain maximum load (see claim 165 "effective amount ... $1X10^8$"; "As the vectors are highly specific and super-infective, the difference between the number of infecting bacteria found at the target tumor cell as compared to the non-cancerous counterparts becomes larger and larger as the dilution of the microorganism culture is increased" (col. 24, lines 43-47; see col. 16, lines 48-51"microorganism becomes co-localized with the tumor and/or infects the tumor cells"; also see claim 9)

Step C) **Harvesting** the bacterial vaccine vector (see claims 157 and 162 "(b) isolating a population of super-infective, tumor specific microorganism from the infected tumor cells"; also see, section 6.1.2 "Cycling the microorganism through solid tumors in vivo", see col. 16, line 51-63

> tumor cells, the mice are sacrificed, the tumors excised, weighed and homogenized. An aliquot may be diluted into the proper microorganism growth medium and incubated at the proper growth conditions for 1-2 population doublings to insure the recovery of viable microorganisms for successive inoculations into tumor bearing mice. Further, if the isolated population is to undergo successive inoculations in tumor bearing mice, upon each successive inoculation, the number of microorganisms in the inoculate and the time of infection may be reduced to increase the stringency of selection for tumor-specific isolates. Additionally, the isolated popula- ")

Step D) **repeating** steps A-C with the harvested bacterial vaccine vector (Listeria "repeating" claim 141; see col. 89, claim 135-136, claim 141, claim 143 "genetically engineered", see claim 145,)

teach the importance of phenotypic stability of the bacterial vaccine vectors (col. 27, lines 18-26;section 18.7, col. 64, lines 45-46, :(see section 6.1.2 "Cycling the microorganism through solid tumors in vivo", see col. 16, line 51-63) that are able to express a heterologous antigen. Also see Definitions for "Super-infective" which are detectably infectious to target tumor cells at a ratio of 90:1 relative to wild-type cells (Pawelek et al, brief summary text paragraph 55). The super-infective bacterial strains are stable, as they are "able to distinguish between a cancerous target cell and non-cancerous

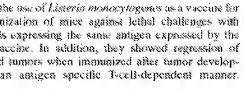
counterpart cell so that the vector preferentially attaches to, infects and/or remains viable in the cancerous target cell.")

and evidence enhanced immunogenicity (specific "Enhancement of tumor immunity is thus another potential advantage in the use of parasites as tumor-specific therapeutic vectors" (col. 58, lines 10-12) and "Subsequent evidence from a number of research laboratories indicated that at least some of the anti-cancer effects are mediated through stimulation of host immune system, resulting in enhanced immuno-rejection of the cancer cells (col. 3, lines 8-12)".

Claims 2, 21: wherein the organ is a liver (see claim 171 "liver cancer") see claim 148, "The present invention is directed to the isolation of novel therapeutic and diagnostic parasitic vectors for solid tumor cancers, ... liver cancer, ...the novel intracellular parasite vectors; methods for the isolation of the novel vectors; genetic engineering of the isolated vectors; and methods for use of the novel vectors as well as other vectors in treatment or detection of solid malignant tumors, including metastatic tumors and tumor cells"

Claims 5-6 , 23-24" wherein the antigen is a tumor antigen (teach (col. 4, lines 29-41) "the use of Listeria monocytogenes as a vaccine for the immunization of mice against lethal challenges with tumor cells expressing the same antigen expressed by the Listeria vaccine. In addition, they showed regression of established tumors when immunized after tumor development in an antigen specific T-cell-dependent manner. .....Pan et al. showed that recombinant Listeria monocytogenes has the ability to deliver a **foreign** antigen to the immune system and to involve cell-mediated immunity against the same antigen." Pan et al., 1995, "A recombinant Listeria Monocytogenes vaccine expressing a model tumour antigen protects mice against lethal tumour cell challenge and causes regression of established tumours", Nature Medicine 1:471-477. "

Instant claim 5-6 , 23-24 : teach Listeria as a bacterial vaccine vector: see col. 89, claim 135-136, claim 141, claim 143 "genetically engineered", see claim 145 "repeating" claim 141,


described the use of *Listeria monocytogenes* as a vaccine for the immunization of mice against lethal challenges with tumor cells expressing the same antigen expressed by the Listeria vaccine. In addition, they showed regression of established tumors when immunized after tumor development in an antigen specific T-cell-dependent manner.

see col. 4, lines 30-33;

Instant claim 9, 27: administered via oral, parenteral (col. 29, lines 32-36"The vectors of the present invention can be **administered** by a number of routes, including but not limited to: orally, topically, injection including, but limited to intravenously, intraperitoneally, subcutaneously, intramuscularly, intratumorally, i.e., direct injection into the tumor, etc").

4. Pawelek et al selects for enhanced adhesiveness, super infectivity, intracellular survivial and enhanced proliferative abilities inside the tumor cells, the adhesiveness, infectivity and survival characteristics all being types of enhanced virulence factors which permit the vaccine vector to expresses the desired heterologous/foreign gene product over a longer period of time (see col.15, lines 57-58: " the microorganism population isolated has enhanced **survival** and/or proliferative abilities inside the tumor cells as compared to the starting population of microorganisms".

5. Pawelek et al shows levels of bacteria per tumor that are shown in Applicant's figure 1 and 2 which are described as being maximum load levels. While Pawelek et al does not use the term maximum load, the mouse passaged bacteria were present at a maximum level 10 X $10^{6 \text{or } 7}$ see Table 9 below.

mice. The procedure was repeated through 4 cycles of infection into mice, followed by recovery from tumors. At the beginning of each cycle, the number of bacteria inoculated and the time of infection was reduced from the previous cycle in order to increase the stringency of selection for tumor-specific mutants. The resultant population recovered after 4 cycles was designated #72^{pop-1}. The results of this procedure are detailed in Table 9 below.

TABLE 9

SELECTION FOR MELANOMA-SPECIFIC *SALMONELLA TYPHIMURIUM* IN TUMOR-BEARING MICE

Infection Cycle	Total # Bacteria Inoculated/mouse	Infection Time	Total # Bacteria Recovered in Tumors*
1	1×10^{10}	120 min	2.1×10^{7}
2	1×10^{9}	80 min	1.6×10^{6}
3	6×10^{8}	60 min	1.7×10^{6}
4	2×10^{6}	40 min	1.4×10^{5}

*Infecting Salmonella were pooled from 4–8 separate tumors for each cycle

6.

Pawelek et al describes repeating the claimed methods steps (see claims 136, 141, 143, 145), and therefore produced strains of bacterial vaccine vectors that would have the same or equivalent functional characteristics based upon the carrying out the same or equivalent methods steps based upon successive administration, passage and harvesting of the bacterial vaccine vectors to achieve "super infective" bacterial strains

Pawelek et al claims a method that utilizes a recombination/genetic engineered Listeria monocytogenes (see claims 135-136, 178-180, 188) that express a heterologous gene products (detailed description paragraph 63), produced by a process that comprises the instant methods steps of administering, passaging, harvesting and repeating, shows maximum load levels of passaged Salmonella tumor specific strains (Table 9), teach Listeria monocytogenes to be a known bacterial vaccine vector for expression of tumor antigens for stimulation of an immune

response, but differs from the instantly claimed invention by failing to show the selection of a Listeria bacterial vaccine vector based upon the described guidance exemplified for Salmonella vectors, the heterologous antigen being a tumor antigen recombinantly expressed by a maximum load selected Listeria vaccine vector.

Vahidy et al teach a maximum load selection process for animal passaged Listeria monocytogenes which results in increased viability counts per gram of infected organ with each passage in an analogous art for the purpose of showing maximum load (see Figure 2, page 141, top of column 1) is a function of infectivity (colonies per gram of infected organ) and virulence operon activation (see page 142, col. 1, paragraph 2, middle of paragraph).

Pan et al teach Listeria recombinant that express a heterologous tumor antigen in an analogous art for the purpose of showing Listeria monocytogenes induces a protective cytolytic T-cell (see Figure 4, title) response when engineered to stably express a foreign/heterologous antigen which stimulates an immune response to the expressed antigen (see abstract and entire article).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to carry out the maximum load selection process taught by Vahidy et al for the Listeria monocytogenes bacterial vaccine vector as taught by Pawelek, because Vahidy et al teach that through animal passage of Listeria monocytogenes the count per gram of infected organ increases to maximum load levels which would provide for stimulation of an enhanced immune response to an encoded heterologous antigen taught by either Pan et al (tumour antigen) or Pawelek et al (tumor antigen or enzyme).

It also would have been obvious to the person of ordinary skill in the art at the time the invention was made to transform Listeria monocytogenes with the heterologous gene coding sequence of an antigen as taught by Pan et al or Pawelek and to carry out animal passaging to maximum load as taught by Vahidy et al because Vahidy et al teaches through maximum load animal passaging increased infectivity results and Pawelek et al is directed to the selection of the super-infective strains that have enhanced **survival** and/or proliferative abilities inside the tumor cell, the enhanced survival providing for an extended period of time for expression of the encoded heterologous antigen

It is prima facie obvious to make a simple substitution of one known equivalent element, passaging for selecting super-infective strains as taught by Pawelek , for another, specifically the maximum load selection process as taught by Vahidy et al, to obtain predictable results. Additionally, it would be prima facie obvious to make a simple substitution of one known equivalent element, specifically the substitution of one heterologous coding sequence for another, to be expressed by an equivalent Listeria monocytogenes bacterial vaccine vector, the Listeria monocytogenes bacterial vaccine vector encoding a heterologous gene sequence being substituted with an antigen (Pan et al) or tumor antigen (Pawelek) and selected for based upon maximum load (Vahidy et al) and stabily (Pawelek) to insure the stimulation of an a strong immune response directed against the antigen (Pan et al) or tumor antigen (Pawelek) expressed by the Listeria monocytogenes maximum load selected vector.

Pawelek in view of Vahidy et al and Pan et al obviate the instantly claimed invention as now claimed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, 5, 7-9, 20-21, 23, 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. All of the claims have been amended to recite the phrase "virulence is stabilized".

10. Upon consideration of the instant Specification and the original claims for original descriptive support for this phrase, none could be found.

11. While the instant Specification teaches passaging a bacterial vaccine vector for the purpose of increasing virulence, the instant Specification does not teach nor describe " virulence is stabilized" when passaged. (see quoted section of instant Specification below:

> Page 11, lines 20-25 "Further, the data disclosed herein demonstrate that passaging a bacterial vaccine vector, such as a Listeria vaccine vector, increases the virulence of the bacterial vaccine vector, as measured by, inter alia, an increased bacterial load provides for increasing the expression of virulence factors"

Applicant did not point out where in the instant Specification the phrase "virulence is stabilized" finds original descriptive support. All of the claims recite New Matter as the functional characteristic "virulence is stabilized" does not evidence original descriptive support in the instant Application at the time of filing.

12. Claims 1-2, 5, 7, 9, 20-21, 23, 25, 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-2, 5, 7, 9, 20-21, 23, 25, 27 are directed to a method that requires the passaging of a bacterial vaccine vector through an animal, and in claims 7 and 25, this animal is claimed to be a mammal.

Upon consideration of the instant Specification for what animals are encompassed by the claims, the Examiner found at page 17, lines 31-33 and page 19, lines 25-30, the animal to include humans "Subjects ..... of the invention is contemplated include, but are not limited to, **humans** ....e")

13. All of the claims require the methods steps of harvesting the bacterial vaccine vector from the animal to include such organs as a spleen or a liver. Harvesting a bacterial vaccine vector from a living human by harvesting infected organs would not be permitted in the United States, therefore the claimed methods are not enabled for using any animal/mammal. Amendment of the claims to recite ----non-human animal---- could obviate this rejection.

Conclusion

This is a non-final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Patricia Duffy can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
December 27, 2010

/Mark Navarro/
Primary Examiner, Art Unit 1645